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Did covid-19 come from a lab?

Could the coronavirus have sprung from a lab or did it pass to humans from an animal? The evidence is out there, but it could be difficult to locate, says **Graham Lawton**

BEFORE heading off to China as leader of a World Health Organization (WHO) fact-finding mission into the origins of SARS-CoV-2, Peter Ben Embarek recorded an explainer video outlining the state of knowledge at the time, January 2021.

"We know that the first human cases that were detected were detected in Wuhan in December 2019," he said. "We also know that this virus belongs to a group of viruses that have their original niche in bat populations. In between these two points, we don't know much."

Five months on, we actually know less, with the two "knowns" now being called into question. Even though Embarek's investigation concluded that one of the possible origins of SARS-CoV-2 – accidental release from a laboratory – was "extremely unlikely", that possibility still hasn't been ruled out. If anything, the case for a lab leak has grown stronger.

On 23 May, *The Wall Street Journal* claimed that US intelligence has evidence of several employees of the Wuhan Institute of Virology, which carries out research on bat coronaviruses, being hospitalised with a respiratory illness similar to covid-19 in November 2019. US President Joe Biden subsequently

"If there was a piece of good evidence for the lab leak hypothesis, we'd pivot quickly"

ordered the US intelligence community to pursue a definitive conclusion on whether the virus spilled naturally from a wildlife reservoir, or from a lab.

The origin of the virus remains one of the most important unknowns of the pandemic.



Workers at Huanan Seafood Market in Wuhan, China

"We need to know where it came from," says David Robertson, an evolutionary virologist at the University of Glasgow, UK. "We have to be worried that that could happen again."

So what is the evidence for and against a laboratory leak? And what pieces of additional evidence are required for a definitive conclusion on the matter?

For now, there is a near-consensus that SARS-CoV-2 had a natural origin in a wild animal, says microbiologist Rossana Segreto at the University of Innsbruck in Austria.

That consensus is the one strongly favoured by Embarek's WHO investigation. At a press conference at the end of the

mission in Wuhan on 9 February, he said that the virus seems to have originated in bats.

However, on 4 March, a group of scientists published an open letter in *The New York Times* calling for an independent investigation on the grounds that the WHO "did not have the mandate, the independence, or the necessary accesses to carry out a full and unrestricted investigation into all the relevant SARS-CoV-2 origin hypotheses". Governments of 14 countries subsequently expressed concern that the WHO "lacked access to complete, original data and samples".

Last month, *Science* published a letter from 18 distinguished scientists, which argued that theories of accidental lab release and so-called zoonotic spillover (where an infectious disease jumps from an animal to a

human) "both remain viable".

One of the signatories is David Relman at Stanford University in California, who argues that the lab-leak hypothesis must be investigated if only to debunk it. "There's still a lot of scientists who are locked into the assumption that this can only have a natural origin," he says. "I'm not quite sure why."

The lab-leak scenario

A lot of the doubts are fuelled by dissatisfaction with the WHO investigation and suspicion of ulterior motives in China. The WHO team had a "really difficult job", says Robertson, because "the Communist party of China want to project it out of China".

But there are also scientific reasons to question the consensus. The lab-leak



hypothesis usually points the finger at the Wuhan Institute of Virology, which is close to the Huanan Seafood Market, where the first major cluster of infections occurred. The institute has a history of analysing bat coronaviruses.

“Without evidence of work on a closely related virus to the one that ‘escaped’, it’s just a conspiracy theory”

The leak scenario involves researchers tinkering around with a virus, perhaps in “gain of function” experiments in which pathogens are modified to be more harmful in a bid to understand them better. This modified virus then somehow slipped through the lab’s biosafety net, which has been criticised by many for being full of holes.

Robertson points out that there is no documented evidence of such experiments taking place. The WHO team granted access to the institute found none. The Wuhan Institute of Virology has reported working with a virus called RaTG13, which is the closest-known relative of SARS-CoV-2. But this is genetically quite distant and RaTG13 clearly isn’t its immediate progenitor, says Robertson. “They weren’t working on the right viruses,” he says.

That, of course, doesn’t rule out undocumented experiments. There are reasons to believe that the institute hasn’t always been transparent, says Relman. In November, it published an addendum to a *Nature* paper revealing that sampling missions to a mine in Yunnan Province where RaTG13 was discovered also yielded eight previously unknown SARS-like coronaviruses. The addendum didn’t give any further details. The institute was alerted

to the Yunnan site in 2012 when four miners fell ill with a respiratory illness after going into the mine to clean up bat guano. One miner died. The institute subsequently confirmed that the men weren’t infected with SARS-CoV-2, but hasn’t determined what caused the illness.

The original omission, and subsequent admission, of this information hasn’t been explained, says Relman. *New Scientist* emailed Zheng-Li Shi, head of bat coronavirus research at the institute, for comment, but she didn’t reply.

But to go from there to positing secretive experiments that ended horribly is to enter the realms of speculation, says Robertson. “It loses all meaning at that point because it’s not about facts any more. Unless you have evidence that they were working on viruses very closely related to the one that ‘escaped’, then that’s where it becomes conspiracy theory.”

However, proponents of the lab-leak hypothesis can point to some arcane details of the virus’s molecular biology. Taken together, they challenge the natural origin

Investigators from the WHO at the Wuhan Institute of Virology earlier this year



REUTERS/THOMAS PETER

hypothesis, argues Segreto.

For example, the virus has a “furin cleavage site”, a part of the spike protein that helps it to break into host cells. Many coronaviruses have this, but SARS-CoV-2 is the only member of its sub-genus *Sarbecovirus* to have one.

Another region of the spike protein, the “receptor binding motif”, appears to be oddly adapted to latch on to human cells. This adaptation was also observed in the original SARS virus, SARS-CoV-1, but only long after it had jumped to humans. The Wuhan strain of SARS-CoV-2 had it from the get-go.

These and other molecular peculiarities are consistent with a virus that has been manipulated in the laboratory, says Segreto.

Not so fast, says Robertson. “The ‘it doesn’t look like it’s natural’ claim is preposterous, because you can find all of those features in natural viruses”. The superficial appearance of unnaturalness arises, says Robertson, due to “recombination”. In a mammal cell co-infected with two coronaviruses, bits of both viral genomes can become stitched together in novel combinations. This can cause incongruous molecular features

to suddenly appear as if by design.

“What’s clear is that SARS-CoV-2 is really just another sister lineage to that first SARS virus,” says Robertson. As for “pre-adaptation”, Robertson says the virus merely evolved to be a generalist, enabling it to extend its natural range beyond bats and into other mammals, which just so happens to include humans, and some other animals.

Follow the science

Robertson admits that the smoking gun of the natural origin hypothesis is also absent. That would be a naturally occurring virus that is genetically close enough to SARS-CoV-2 to plausibly be its direct ancestor. “It remains most likely that the immediate ancestor to SARS-CoV-2 exists in the wild and is still to be found,” says Jonathan Stoye at the Francis Crick Institute in London.

But searching for such a progenitor will be difficult. Bats carrying SARS-like coronaviruses live right across China and into South-East Asia, and current levels of sampling aren’t adequate.

Robertson is also at pains to point out that he and his colleagues will follow the science where it leads. “If there was a piece of good evidence [for the lab leak hypothesis], we would pivot on that very quickly.”

All things considered, both hypotheses have to be left on the table for now. Work is ongoing to reject one or the other, not least by Embarek’s WHO team, which continues with investigations. Biden has given his intelligence agencies 90 days to report back. However, it took a decade to discover the origins of SARS-CoV-1, which was unimpeded by geopolitical intrigue. So don’t expect an answer any time soon. ■